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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/049,502	02/15/2002	Said M. Sebti	15101.01902	7653

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SALIWANCHIK LLOYD & SALIWANCHIK
A PROFESSIONAL ASSOCIATION
PO BOX 142950
GAINESVILLE, FL 32614-2950

EXAMINER	
MARVICH, MARIA	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 06/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/049,502	SEBTI, SAID M.	
	Examiner	Art Unit	
	Maria B. Marvich, PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-12 and 16-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-12 and 16-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/1/04*.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *4/05*.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to a response to an amendment and Declaration under 37 CFR 1.132 filed 12/17/04 and an amendment filed 4/12/05. Claims 1-6 and 13-15 have been canceled. Claims 17-34 have been added. Claims 7-12 and 16 have been amended. Claims 7-12 and 16-34 are pending in the application.

The Declaration under 37 CFR 1.132 filed 12/17/04 is sufficient to overcome the rejection of claims based upon 35 USC 102(a).

Response to Amendment

Any rejection of record in the previous action not addressed in this office action is withdrawn. The are new grounds of rejection herein that were not necessitated by amendment and, therefore, this action is non-final.

Information Disclosure Statement

An Information Disclosure Statement filed 6/1/04 has been identified and the document considered. The signed and initialed PTO Form 1449s has been mailed with this action.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101, which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or

improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 7, 16, 17, 19, 27, 28, 30 and 32 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 2-12 and 15 of copending Application No. 10/759328. **This is a new rejection.**

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claims because the examined claim is either anticipated by, or would have been obvious over, the reference claims. Although the conflicting claims are not identical, they are not patentably distinct from each other because the cited claims of the instant invention are generic to all that is recited in claims 2-12 and 15 of the copending Application No. 10/759328. That is, the cited claims of 10/759328 anticipate and fall entirely within the scope of the rejected claims of the instant application. Specifically, both applications recite a method of inhibiting (suppressing) cancer cell growth by contacting the interior of a cell with RhoB protein or using a nucleic acid encoding RhoB.

Additionally, if a patent resulting from the instant claims was issued and transferred to an assignee different from the assignee holding the 10/759328 application, then two different

assignees would hold a patent to the claimed invention of 10/759328 application, and thus improperly there would be possible harassment by multiple assignees.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 21 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new rejection necessitated by applicants' amendment. This is a New Matter Rejection.**

The limitation the nucleic acid is introduced "locally" has been added to claim 21. Applicant has not indicated where support for this limitation is found. The examiner has been unable to find literal or inherent support in the originally filed specification for the term "locally". Therefore, the limitation that the nucleic acid is introduced "locally" is impermissible NEW MATTER.

Claims 7-12, 16-18 and 20-34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *in vitro* contacting of the interior of a cell with RhoB protein to suppress growth and malignant transformation of a cell, suppress tumor growth,

induce apoptosis and decrease phosphorylation of Akt and Erk2 and for inhibition of tumor growth in mouse xenograft models does not reasonably provide enablement for *in vivo* contacting of a cell with RhoB protein or variants for the aforementioned processes or for combination therapy with RhoB and at least one additional therapy. Furthermore, the specification does not reasonably provide enablement for preventing malignant transformation. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. **This rejection is maintained for reasons of record in the office action mailed 8/11/04 and restated below. This rejection is extended to newly added claims 17, 18 and 20-34.**

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

1) **Nature of invention**. The invention is directed towards methods of cancer or oncogenic therapy using RhoB or variants thereof. The invention utilizes disciplines of molecular biology, cell biology and clinical technology.

2) **Scope of the invention**. The claims specifically recite methods of inhibiting growth of a cancerous cell, suppression of malignant transformation, inhibition of tumor growth, induction of apoptosis in a transformed cell, inhibition of oncogenic signaling, prevention of

malignant transformation, decreasing phosphorylated protein in a transformed cell, suppressing growth of cancerous cells or inhibiting cell growth in combination with one additional therapy. Each of these goals is met by the step of administering RhoB to the cell. Applicants disclose that a use of these methods is in gene therapy, which exacerbates the lack of guidance associated with meeting the goals of such varied methods. Furthermore, applicants recite that malignancy transformation is prevented. Prevention of any disease is an unpredictable art.

3) **Number of working examples and guidance**. Applicants recite methods of inhibiting growth of a cancerous cell, suppression of malignant transformation, inhibition of tumor growth, induction of apoptosis in a transformed cell, inhibition of oncogenic signaling, prevention of malignant transformation, suppressing growth of cancerous cells and decreasing protein phosphorylation in a transformed cell by contacting a cell interior with RhoB or variants thereof. Applicants teach that RhoB protein or variants thereof denotes RhoB-F, RhoB-GG and RhoB-WT proteins. As well the methods can involve an additional therapy such as chemotherapy, radiation therapy and therapy that selectively inhibits Ras oncogenic signaling.

Panc-1 and A549 cell cultures were transfected with constructs expressing RhoB, RhoB-F and RhoB-GG. Cells expressing these constructs exhibited reduced foci formation and little growth in soft agar. Hence RhoB was accorded a role in antagonizing tumor growth and malignant transformation. The transfected cells exhibited enhanced apoptosis and decreased phosphorylation of Akt and Erk2. Foci formation was also decreased in C-33A, Hela and Saos-2 cells transfected with RhoB. Applicants then demonstrated that Panc-1 cells expressing RhoB exhibited suppressed tumor growth in nude mice. Based upon these observations, applicants recite a variety of therapeutic approaches based upon administration of RhoB to a cell to inhibit

cancer cell growth, transformation, apoptosis, tumor growth, oncogenic signaling, protein phosphorylation and in combination with an additional therapy inhibition of cancer cell growth.

Guidance for in vivo administration of RhoB is broad and general except to describe use of recombinant viral vectors such as retroviruses are used as a delivery vehicle of RhoB nucleic acids. The guidance is more a general review of the art related to *in vivo* methods. Applicants' disclosure lacks any guidance for the methods of combining RhoB therapy with an additional therapy such as chemotherapy or radiotherapy.

4) **State of Art** The instant invention recites that RhoB can contact the interior of the cell following administration of either nucleic acid encoding RhoB or RhoB protein. Administration of nucleic acids utilizes the art of gene therapy, which is a highly unpredictable art.
Three major obstacles for gene therapy are 1) gene expression 2) gene delivery and 3) efficacy and toxicity of administration (Meng and El-Deiry, 1999). Vector based and non-vector based means of introducing the DNA into the cell to be expressed have not successfully overcome any of these obstacles. The route of delivery itself presents an obstacle to be overcome for the application of the vector therapeutically. Verma and Somia (1997) teach, "The Achilles heel of gene therapy is gene delivery. . . the problem has been an inability to deliver genes efficiently and to obtain sustained expression". No modes of gene administration were proposed in the specification including means and routes of administration except to generally refer to gene expression vectors and retrovirus. To date, no single mode of gene transfer has provided a viable option for successful gene therapy protocols. As noted by Marshall, (Marshall et a1, Science January 17, 2003) one of the main issues in using retroviral vectors for gene therapy is determining how to use the vector in vivo without causing leukemia or other cancers in the

patients being treated. This is not merely a safety issue for FDA concern but is a fundamental issue underlying how the skilled artisan can make and use the claimed invention for the recited treatments.

The art of protein therapy also is highly unpredictable. Torchilin and Lukyanov (2003) teach that there are many unresolved problems concerning the delivery of proteins and peptides such as rapid elimination from the circulation through renal filtration, enzymatic degradation, and uptake by the reticuloendothelial system and accumulation in non-targeted organs and tissues and inefficient cell entry (see Box 1, page 260).

5) Unpredictability of the art. The unpredictable nature of administration of RhoB nucleic acid or protein in vivo is exacerbated due to the lack of recited methods. Many parameters must be addressed for in vivo gene or protein delivery such as lack of toxicity to normal tissues, and the effect of the immune response as well as doses to be administered, dose schedules etc. For example, what level of expression or protein is necessary to achieve therapeutic affects without toxicity to normal cells that results from leaky expression of the viral gene required for replication?

Applicants demonstrate a potential role for RhoB in multiple processes such as malignant transformation and apoptosis and even tumor growth in nude mice. However, historically in vitro and animal models have not correlated well with in vivo clinical trial results in patients. It is not clear that reliance on experimental models accurately reflects the relative superiority or efficacy of the claimed therapeutic strategy and applicants present no disclosed or art recognized nexus between the xenograph and nude mice experimental models and the human disease state. "Although animal studies have suggested low toxicity and excellent efficacy, these investigation

have been limited by the use of immuno-deficient mice" (Meng and Diery p. 6, column 1). The success of any in vitro assays or in vivo animal models cannot be considered as evidence of success of treatment, *in vivo* results rarely correlate well with in vivo clinical trial results in patients and have not translated into successful human therapies. Many *in vitro* and animal models that are provided as evidence of success of treatment have not translated into successful treatments in humans.

Applicants recite a method of preventing malignant transformation. The process of preventing disease is highly unpredictable. In humans, the claimed diseases are usually established before therapy is offered. The specification does not adequately teach how to effectively predict for whom prevention would be required. The lack of well defined targets (i.e. for whom the disease is prevented) compounded by the lack of disclosure for treatment with RhoB makes it unpredictable as how to determine patients most likely to benefit from treatment, how to deliver to multiple targets, when to deliver, how to keep the drug in place long enough to achieve %11 activity and how to overcome the potential deleterious effects of inhibition of wound healing.

6) Summary. The invention recites a single method step for of inhibiting growth of a cancerous cell, suppression of malignant transformation, inhibition of tumor growth, induction of apoptosis in a transformed cell, inhibition of oncogenic signaling, prevention of malignant transformation and decreasing phosphorylation of protein in a transformed cell. The unpredictability of using the claimed invention in therapy is accentuated due to the lack of methods or processes disclosed in the instant specification that exacerbates a highly unpredictable art.

In view of predictability of the art to which the invention pertains and the lack of: undue experimentation would be required to practice the claimed methods with reasonable expectation of success, absent a specific and detailed description in the specification. Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be concluded that the skilled artisan would have had to conduct undue, unpredictable experimentation in order to practice the claimed invention.

Response to Argument

Applicants traverse the claim rejections under 35 U.S.C. 112, first paragraph on pages 8-14 of the amendment filed 12/17/04. Applicants argue the following. 1) Post-filing data demonstrates that RhoB is potent tumor suppressor. Specifically, the provided experimental data utilize a viral vector construct encoding RhoB delivered *in vivo* to a mouse model injected with A549 human lung tumor cells resulting in inhibited tumor growth. Applicants argue that combined with what was understood about RhoB function and commensurate with suppressed or inhibited tumor growth, RhoB would be expected to induce apoptosis of transformed cells, inhibit oncogenic signaling, decrease phosphorylation of Akt1, Erk1 and Erk2 within transformed cells. Therefore, the data is reasonably predictive of RhoBs therapeutic benefit. Applicants argue that the nude mouse xenograft model is a well-recognized model of cancer that is recognized by those in the field as one of the best tools for conduct pre-clinical *in vivo* analyses of intact human tissue. 2) Applicants argue that the specification is enabling for a variety of means of introducing RhoB. Robson et al demonstrate that multiple methodologies and vectors are available for *in vivo* treatment of cancer. Combined with the reported successful

delivery and expression of p53 *in vivo*, applicants argue that the obstacles to RhoB delivery could be addressed by optimization and not undue experimentation. To this end, applicants cite several means of targeting and encapsulation technologies available at the time of filing. For example, peptides that are highly basic and hydrophilic, liposomes, antibodies, pvp nanoparticles and maleylated bsa have the ability to transport proteins across the cell membrane and enter the cell. The efficacy of transported molecules in these studies was demonstrated *in vitro* and *in vivo*. As well, applicants argue that there is no evidence that RhoB is toxic to cells. 3) Applicants argue that there is much evidence that combination therapy is operative for cancer treatment and no technological hurdle exists for combination of RhoB with conventional combination therapy. 4) Applicants argue that an application need not show that a claimed method of treatment of a disease condition results in a cure of the disease condition or that clinical efficacy is achieved. As support, applicants cite Federal Circuit rulings that a showing for therapeutic utility that is sufficient is not the same as required for FDA approval. 5) Applicants argue that introduction of RhoB into normal cells can prevent malignant transformation as RhoB blocks Ras, EGFR and ErB2-mediated malignant transformation.

Applicants' arguments filed 12/17/04 have been considered but are not persuasive.

1) Given the lack of guidance in the specification, the large and diverse group of treatments recited and the highly unpredictable nature of the art, it is concluded that a person of skill in the art would have had to conduct undue experimentation in order to practice the claimed invention. Applicants post-filing data demonstrates that delivery of RhoB to a mouse model leads to a decrease in tumor growth over a 16-day period. Therefore, the instant invention relies on experiments utilizing *in vitro* and animal models as well as observations in the art regarding

RhoB function to formulate an *in vivo* application of RhoB for a variety of applications. As the provided teachings demonstrate, it is well known in the art that the field of therapy based upon biomolecules is in general highly unpredictable made more so by the multi-faceted and complex nature of cancer. It is not clear that reliance on experimental models accurately reflects the relative superiority or efficacy of the claimed therapeutic strategy and applicants present no disclosed or art recognized nexus between the xenograft and nude mice experimental models and the human disease state. "Although animal studies have suggested low toxicity and excellent efficacy, these investigation have been limited by the use of immuno-deficient mice" (Meng and Deiry, Gene Therapy of Cancer, 1999, p. 6, column 1). The success of any *in vitro* assays or *in vivo* animal models cannot be considered as evidence of success of treatment, *in vitro* results rarely correlate well with *in vivo* clinical trial results in patients and have not translated into successful human therapies. Gura in a study by the National Cancer Institute has observed that mice did no handle drugs in the same way that humans do. Furthermore, cell culture was not an adequate indicator that the drug would reach its target. Ultimately the mouse model predicts agents that are effective in treating mice but not humans (see Gura, e.g. page 1041, col 1 and col 2, last paragraph). Therefore, the ability to predict potential success in humans based upon experimental results is highly unpredictable as demonstrated by the art.

2) Neither the specification nor the prior art provides guidance on appropriate means of delivery of RhoB protein to a subject or an indication that such therapy has the potential to deliver adequate amount of protein to a subject that is not cleared by normal or allergic responses. Furthermore, while evidence has not demonstrated that RhoB is toxic to cells, a persistent problem for gene therapy is adequate levels of the therapeutic protein without

clearance or toxicity of surrounding cells (see e.g. Torchilin, box 1). The art has not demonstrated that this general problem has been solved to date. The prior art teaches that means of administration as described by Torchilin are persistent problems for therapy based upon biomolecules. The art has demonstrated through numerous publications such as those cited above that use of viral vectors *in vivo* is highly unpredictable for successful human therapy.

The potential of gene therapy has long been recognized however not realized. The publications cited by the applicants and particularly Robson et al attest to this potential. The realization of use of viral vectors or protein therapy for gene therapy is not advanced by these publications for human use. Specifically, the cited publications teach transport *in vitro* or to animal models. It is noted that US PN 6,674,980 is not drawn to TAT peptides as stated. However, given the unpredictability of human administration as described above, the use of these methods in humans is highly unpredictable. While applicants have argued that p53 has been successfully delivered and expressed *in vivo* these results are difficult to evaluate without the corresponding references.

3) The rejection under 35 USC 112, first paragraph only indicates that the specification does not teach any guidance for combination therapy but does not specifically state that these methods lack guidance in the art. Furthermore, the rejection does not indicate that combination therapy itself is highly unpredictable. 4) The Federal Circuit rulings applicants have cited regard utility. The rejection of the instant claims is for lack of enablement. While applicants have argued that the state of the art with the experimental data demonstrates that undue experimentation is not required. However, the data and specification have only demonstrated that undue experimentation is not required for administration of the compounds *in vitro* and to animal

models. 5) Applicants argue that the specification is enabled for prevention of malignant transformation. Prevention of a disease state requires knowledge of the subjects for whom prevention is required. The ability to *a priori* determine fro whom therapies would be required is highly unpredictable. Furthermore, to effectively prevent malignant transformation, RhoB would have to be administered for the life of the patient. Risk of overexposure to RhoB, clearance and resistance render the art of prevention highly unpredictable.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B. Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD can be reached on (571)-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maria B Marvich, PhD
Examiner
Art Unit 1636

June 26, 2005

JAMES KETTER
PRIMARY EXAMINER